VASOPRESSIN FORMULATIONS FOR USE IN TREATMENT OF HYPOTENSION

CROSS REFERENCE

This application is a continuation of U.S. application Ser. No. 14/610,499, filed Jan. 30, 2015, which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 20, 2015, is named 47956-702.301_SL.txt and is 5120 bytes in size.

BACKGROUND

Vasopressin is a potent endogenous hormone, responsible for maintaining plasma osmolality and volume in most mammals. Vasopressin can be used clinically in the treatment of sepsis and cardiac conditions, and in the elevation of patient's suffering from low blood pressure. Current formulations of vasopressin require refrigeration for maintenance or reconstitution of lyophilized powders due to vasopressin's poor long-term stability.

SUMMARY OF THE INVENTION

In some embodiments, the invention provides a pharmaceutical composition comprising, in a unit dosage form: a) from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin, or a pharmaceutically-acceptable salt thereof; and b) a polymeric pharmaceutically-acceptable excipient in an amount that is from about 1% to about 10% by mass of the unit dosage form or the pharmaceutically-acceptable salt thereof, wherein the unit dosage form exhibits from about 5% to about 10% less degradation of the vasopressin or the pharmaceutically-acceptable salt thereof after storage for about 1 week at about 60° C. than does a corresponding unit dosage form, wherein the corresponding unit dosage form consists essentially of: A) vasopressin, or a pharmaceutically-acceptable salt thereof; and B) a buffer having acidic pH.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a chromatogram of a diluent used in vasopressin assay.

FIG. **2** is a chromatogram of a sensitivity solution used in a vasopressin assay.

FIG. **3** is a chromatogram of an impurity marker solution used in a vasopressin assay.

FIG. **4** is a zoomed-in depiction of the chromatogram in FIG. **3**.

FIG. **5** is a chromatogram of a vasopressin standard solution.

FIG. **6** is a chromatogram of a sample vasopressin preparation.

FIG. **7** is a UV spectrum of a vasopressin sample.

FIG. **8** is a UV spectrum of a vasopressin standard.

FIG. **9** plots vasopressin stability across a range of pH as determined experimentally.

FIG. **10** illustrates the effects of various stabilizers on vasopressin stability.

DETAILED DESCRIPTION

Vasopressin and Peptides of the Invention

Vasopressin, a peptide hormone, acts to regulate water retention in the body and is a neurotransmitter that controls circadian rhythm, thermoregulation, and adrenocorticotrophic hormone (ACTH) release. Vasopressin is synthesized as a pro-hormone in neurosecretory cells of the hypothalamus, and is subsequently transported to the pituitary gland for storage. Vasopressin is released upon detection of hyperosmolality in the plasma, which can be due to dehydration of the body. Upon release, vasopressin increases the permeability of collecting ducts in the kidney to reduce renal excretion of water. The decrease in renal excretion of water leads to an increase in water retention of the body and an increase in blood volume. At higher concentrations, vasopressin raises blood pressure by inducing vasoconstriction.

Vasopressin acts through various receptors in the body including, for example, the V1, V2, V3, and oxytocin-type (OTR) receptors. The V1 receptors occur on vascular smooth muscle cells, and the major effect of vasopressin action on the V1 receptor is the induction of vasoconstriction via an increase of intracellular calcium. V2 receptors occur on the collecting ducts and the distal tubule of the kidney. V2 receptors play a role in detection of plasma volume and osmolality. V3 receptors occur in the pituitary gland and can cause ACTH release upon vasopressin binding. OTRs can be found on the myometrium and vascular smooth muscle. Engagement of OTRs via vasopressin leads to an increase of intracellular calcium and vasoconstriction.

Vasopressin is a nonapeptide, illustrated below (SEQ ID NO. 1):

At neutral to acidic pH, the two basic groups of vasopressin, the N-terminal cysteine, and the arginine at position eight, are protonated, and can each carry an acetate counterion. The amide groups of the N-terminal glycine, the glutamine at position four, and the asparagine at position five, are susceptible to modification when stored as clinical formulations, such as unit dosage forms. The glycine, glutamine, and asparagine residues can undergo deamidation to yield the parent carboxylic acid and several degradation products as detailed in EXAMPLE 1 and TABLE 1 below.

Deamidation is a peptide modification during which an amide group is removed from an amino acid, and can be associated with protein degradation, apoptosis, and other regulatory functions within the cell. Deamidation of asparagine and glutamine residues can occur in vitro and in vivo, and can lead to perturbation of the structure and function of the affected proteins. The susceptibility to deamidation can depend on primary sequence of the protein, three-dimensional structure of the protein, and solution properties including, for example, pH, temperature, ionic strength, and buffer ions. Deamidation can be catalyzed by acidic conditions. Under physiological conditions, deamidation of asparagine occurs via the formation of a five-membered succinimide ring intermediate by a nucleophilic attack of the nitrogen atom in the following peptide bond on the carbonyl group of the asparagine side chain. Acetylation is a peptide modification whereby an acetyl group is introduced into an amino acid, such as on the N-terminus of the peptide.

Vasopressin can also form dimers in solution and in vivo. The vasopressin dimers can occur through the formation of disulfide bridges that bind a pair of vasopressin monomers together. The dimers can form between two parallel or anti-parallel chains of vasopressin.